

Resource-demanding versus cost-effective bimanual interaction in the brain

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Abstract When two hands require different information in bimanual asymmetric movements, interference can occur via callosal connections and ipsilateral corticospinal pathways. This interference could potentially work as a cost-effective measure in symmetric movements, allowing the same information to be commonly available to both hands at once. Using functional magnetic resonance imaging, we investigated supra-additive and sub-additive neural interactions in bimanual movements during the initiation and continuation phases of movement. We compared activity during bimanual asymmetric and symmetric movements with the sum of activity during unimanual right and left finger-tapping. Supra-additive continuation-related activation was found in the right dorsal premotor cortex and left

cerebellum (lobule V) during asymmetric movements. In addition, for unimanual movements, the right dorsal premotor cortex and left cerebellum (lobule V) showed significant activation only for left-hand (non-dominant) movements, but not for right-hand movements. These results suggest that resource-demanding interactions in bimanual asymmetric movements are involved in a non-dominant hand motor network that functions to keep non-dominant hand movements stable. We found sub-additive continuation-related activation in the supplementary motor area (SMA), bilateral cerebellum (lobule VI) in symmetric movements, and the SMA in asymmetric movements. This suggests that no extra demands were placed on these areas in bimanual movements despite the conventional notion that they play crucial roles in bimanual coordination. Sub-additive initiation-related activation in the left anterior putamen suggests that symmetric movements place lower demands on motor programming. These findings indicate that, depending on coordination patterns, the neural substrates of bimanual movements either exhibit greater effort to keep non-dominant hand movements stable, or save neural cost by sharing information commonly to both hands.

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Introduction

Bimanual coordination is a common form of multiple-limb coordination often utilized in daily activities such as eating, typing and driving. Bimanual movements are not merely the sum of two unimanual movements, as demonstrated by their stability dramatically changing depending on the particular coordination pattern being performed. The

asymmetric mode of bimanual movement, which requires the simultaneous activation of non-homologous muscle groups, is less stable than the symmetric mode, which requires the activation of homologous muscle groups (Kelso 1984). Callosal connections between the two hemispheres and ipsilateral corticospinal pathways convey the same information to bilateral homologous muscles, so could explain the bimanual interaction (Cardoso de Oliveira 2002). However, the effects of neural connectivity on whole-brain activity—the neural substrates of bimanual interaction—have not been fully investigated at present.

The neural substrates of bimanual interaction are conventionally accepted to manifest as a pattern of greater brain activation during asymmetric than symmetric actions. Increased movement continuation-related activations have been reported in the supplementary motor area (SMA), the dorsal premotor cortex (PMd), parietal lobule, cerebellum and basal ganglia (Sadato et al. 1997; Stephan et al. 1999; Immisch et al. 2001; Meyer-Lindenberg et al. 2002; Aramaki et al. 2006; Kraft et al. 2007), while greater initiation-related activation has been reported in the putamen of the basal ganglia (Kraft et al. 2007). Because the main focus of these previous studies was the way in which complex movements are executed, activation in these areas has often been interpreted as revealing increased demands related to the inhibition of neural crosstalk in asymmetric actions (Sadato et al. 1997; Aramaki et al. 2006; Kraft et al. 2007). However, direct comparison of two modes of bimanual action cannot clarify whether it is the increased demands of asymmetric actions or the reduced demands of symmetric actions that underlies the greater activation observed during asymmetric movements. Because neural crosstalk conveys the same information to both hands, asymmetric movements entail greater processing demands for inhibiting this crosstalk. For symmetric movements, however, this information sharing may function as a cost-effective measure because the same information is required for producing the movements of both hands. This hypothesis predicts a dissociation between resource-demanding (supra-additive) brain areas involved in asymmetric actions and cost-effective (sub-additive) areas involved in symmetric movements. This would be predicted to occur within the areas conventionally associated with bimanual interaction when their activity is compared with the sum of activity related to two unimanual movements. There are, however, few studies comparing activation patterns during bimanual movements with the sum of activity generated during two unimanual movements (Swinen and Wenderoth 2004).

To clarify supra/sub-additive activity involved in bimanual interaction, we compared brain activation during bimanual asymmetric and symmetric finger-tapping with the sum of activity generated during two unimanual finger-tapping tasks.

Bimanual interactions have been reported to occur on two time scales: transient interactions during motor programming, and static interactions during motor execution (Heuer et al. 2001; Cardoso de Oliveira 2002). Because transient interactions would be expected in the movement initiation phase and static interactions would be expected to be involved in the movement continuation phase (Lewis et al. 2004; Kraft et al. 2007), we examined initiation-related and continuation-related bimanual interactions separately.

Methods

Subjects

Seventeen healthy volunteers (age range, 25–38 years; mean age \pm SD, 29.8 ± 4.11 ; ten males, seven females) participated in the present study. The subjects were all right-handed according to the Edinburgh handedness inventory (0.92 ± 0.14 ; Oldfield 1971). None of the subjects had a history of psychiatric or neurological illness. The protocol was approved by the ethical committee of the National Institute of Physiological Sciences, Japan. All participants gave written informed consent before taking part in the study.

Experiment

We used a 30-s periodic bimanual finger-tapping task (Fig. 1a) to examine both the phasic interactions during initiation and the static interactions during the continuation of bimanual movements. Participants completed four conditions: unilateral sequential finger-tapping using the index and middle fingers of the right (UR) and left (UL) hands, and bimanual finger-tapping involving asymmetric (BA) and symmetric (BS) movements (Fig. 1a). We defined BA movements as asymmetric or anti-phase movements resulting from the simultaneous activation of non-homologous muscle groups: the synchronous tapping of the left middle and the right index fingers, which alternated periodically with the synchronous tapping of the left index and the right middle fingers: ($M_{\text{L}} \times I_{\text{R}}$), ($I_{\text{L}} \times M_{\text{R}}$), ($M_{\text{L}} \times I_{\text{R}}$) and so on (Fig. 1a, upper). BS movement was defined as symmetric or in-phase movements of homologous effectors: the synchronous tapping of both index fingers alternating periodically with the synchronous tapping of both middle fingers: ($I_{\text{L}} \times I_{\text{R}}$), ($M_{\text{L}} \times M_{\text{R}}$), ($I_{\text{L}} \times I_{\text{R}}$) and so on (Fig. 1a, lower). Two USB MRI-compatible 10-key pads (TK-UYGT, ELECOM, Japan) were used to record the finger taps. For right-handed finger taps, keys “1” (for the index finger) and “3” (for the middle finger) of the 10-key pad were used. For the left hand, keys “7” (for the index finger) and “9” (for the middle finger) of another 10-key pad were pressed.

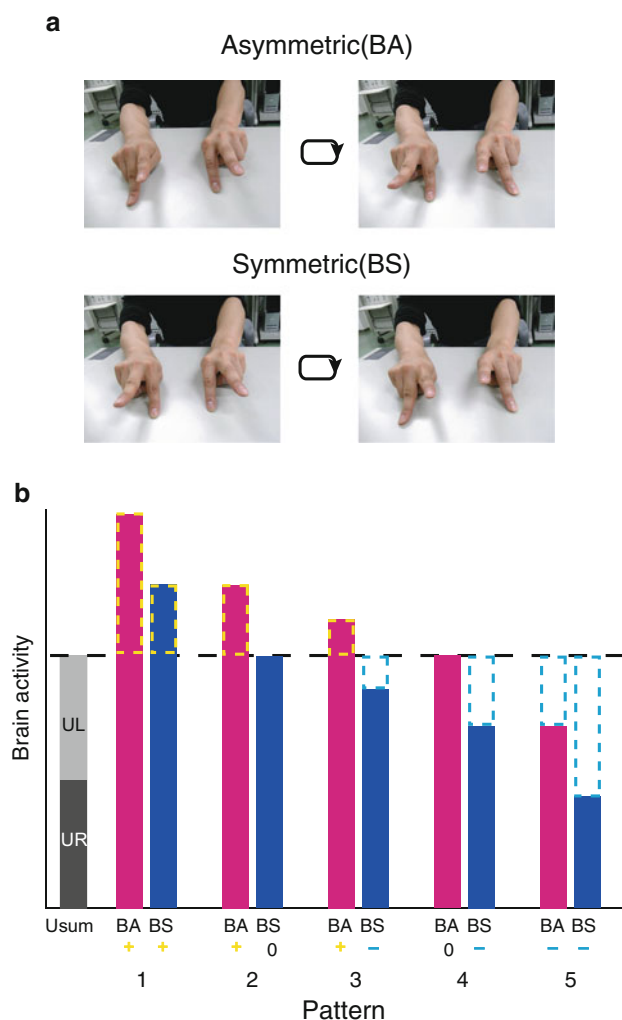


Fig. 1 **a** Bimanual tasks used in the present study. In the asymmetric condition (BA), subjects performed synchronous tapping of the *left middle* and the *right index* fingers, which alternated periodically with the synchronous tapping of the *left index* and the *right middle* fingers. In the symmetric condition (BS), the synchronous tapping of both *index* fingers alternated periodically with the synchronous tapping of both *middle* fingers. **b** Five possible relationships between the brain activity associated with the two bimanual conditions and the sum (Usum) of the *unimanual right* (UR, black) and *left* (UL, gray) conditions, when BA (magenta) shows greater activity than BS (blue): (1) BA and BS activation were greater than Usum, (2) BA was greater than Usum while BS was similar to Usum, (3) BA was greater than Usum while BS was lower than Usum, (4) BA was similar to Usum while BS was lower than Usum, and (5) BA and BS were lower than Usum. Yellow + = increased activity; and cyan — = reduced activity compared with the Usum condition

We were able to use a relatively complex pattern of symmetric versus parallel movement (involving two fingers in each hand) because tapping movements are typically stable and easy to record with a 10-key pad than other tasks often used in fMRI studies, such as abduction/adduction of the index finger. However, one-finger-tapping in each hand cannot match the tapping frequencies of both hands, and the tempo of the whole system between BS and BA. If we

match tapping frequency of each finger between BS and BA movements, the tempo of the whole system for BA movements becomes twice that for BS movements. On the other hand, if we match the tempo of whole system, the tapping frequency of each hand in BS movements becomes twice that in BA movements. Instead, by using two fingers of each hand, we can match both the moving frequency of each finger (1.5 Hz) and the tempo of whole system (3 Hz) between BS and BA conditions.

Auditory cues of 3 Hz were used to keep the tapping frequency constant. In this study, we aimed to make clear differences between BA and BS movements. Thus, we set as high frequency of movement for the participant keeping the BA mode, because previous studies have reported that the higher the pacing frequency, the greater the difference in brain activation between symmetric and asymmetric bimanual movements (Meyer-Lindenberg et al. 2002). However, if the frequency is too high it can make BA movements unstable and cause spontaneous phase transition to BS movements. In a previous study (Aramaki et al. 2006), we found that the average frequency across participants while they kept a BA movement pattern for 20 s was 3.8 Hz. As such, we set the pace of BA movements slightly lower than in our previous study, with a pacing frequency at 3 Hz while participants attempted to keep a BA movement pattern for 30 s.

Each task condition (BA, BS, UR, UL) was performed in separate sessions. The session for each condition consisted of alternating four rest and three task epochs. Each epoch was 30 s in duration. The name of the condition type was visually presented once before each session began. Participants were required to fixate on a crosshair on the screen, so that they could not see their hands. The color of the fixation point changed to green ('go') alternating with red ('stop') every 30 s. The auditory cue was provided continuously throughout the scanning session. Participants performed two sessions per condition, therefore eight sessions in total. The order of the conditions was counterbalanced across participants. Presentation software (Neurobehavioral Systems, Albany, CA) was used to provide the auditory cues and to record the timing of the key-presses at a frequency of 1,000 Hz. To minimize head motion, we used tight but comfortable foam padding placed around the participant's head. An LCD projector (DLA-M200L; Victor, Yokohama, Japan) located outside and behind the scanner projected the crosshair through another waveguide to a translucent screen, which the participants viewed via a mirror attached to the head coil of the MRI scanner.

Behavioral data analysis

We calculated participants' reaction times (RTs), which we defined as the time from the onset cue to the fastest tap.

We also calculated the mean deviation of the inter-tap interval (ITI) from the required ITI (333 ms) for each hand to evaluate the accuracy of the participants' tapping rhythm in each condition. Because we failed to record data for the right hand for five participants, we performed a repeated-measures ANOVA with *post hoc* paired *t*-tests and a Bonferroni correction for multiple comparisons for the RTs and for the right-hand mean ITI deviation using data from 12 participants. The left-hand mean ITI deviation was calculated using data from 17 participants. The threshold of statistical significance was set to $P < 0.05$.

fMRI data acquisition and analysis

A time-course series of 71 volumes was acquired in each session using T2*-weighted gradient echo-planar imaging (EPI) sequences with a 3.0-Tesla MR imager (Allegra; Siemens, Erlangen, Germany). Each volume consisted of 44 axial slices with a slice thickness of 3 mm and no gap, to include the entire cerebral cortex and cerebellum. The time-interval between two successive acquisitions of the same image was 3,000 ms, and the echo time was 30 ms. The flip angle was 85°. The field of view was 192 mm and the in-plane matrix size was 64×64 pixels, with a pixel dimension of 3×3 mm. For an anatomical reference, T1-weighted images were obtained from each participant with location variables identical to those of the EPIs. In addition, three-dimensional (3D) high-resolution T1-weighted images were obtained. A total of 192 transaxial slices were acquired. The in-plane matrix size was 256×256 pixels, the slice thickness was 1 mm, and the pixel size was 0.898×0.898 mm.

For preprocessing and statistical analysis of fMRI data, we used Statistical Parametric Mapping (SPM), version 99 (Wellcome Department of Cognitive Neurology, London, UK) (Friston et al. 1995a, b) implemented in Matlab (Mathworks, Sherborn, MA). The first six volumes of each fMRI session were discarded because of unsteady magnetization. The remaining 65 volumes per participant were used for the analyses. Following realignment of the fMRI data, each 3D high-resolution T1-image was coregistered to the fMRI data using the anatomical T1-weighted images with identical locations to the fMRI data. The parameters for affine and non-linear transformation into the Montreal Neurological Institute (MNI) T1-template image were estimated using the 3D high-resolution T1-image with least-squares means (Friston et al. 1995a). The parameters were then applied to the realigned fMRI data. The anatomically normalized fMRI data were filtered using a Gaussian kernel of 8 mm (full width at half maximum) in the *x*, *y* and *z* axes.

First, we decomposed the brain activity into initiation-related activity and continuation-related activity. Two regressors were included in the general linear model to

detect movement initiation-related brain activity and movement continuation-related activity (supplementary figure). The initiation of movement was expressed as delta functions and hence had no duration. The continuation of movement was expressed as a box-car function with a duration of 30 s. Each neuronal model was convolved with a hemodynamic-response function. To heighten the orthogonality between these two regressors, the movement period was set to 30 s, which was sufficient to separate initiation-related activity from continuation-related activity because the correlation between the two regressors was only 0.04. Our aim was to uncover regions showing increased or reduced brain activity in bimanual movements compared with the sum of activity during right and left unimanual movements (Usum) within the brain areas highlighted by the conventional comparison between BA and BS movements. Thus, we generated BA > BS brain maps for initiation-related activity (INI) and continuation-related activity (CON), and tested the contrasts [INI_BA(1) > INI_BS(−1), inclusively masked with the INI_BA(1) > rest(0) brain image] and the contrast [CON_BA(1) > CON_BS(−1), inclusively masked with the CON_BA(1) > rest(0) brain image], respectively. Finally, using these brain maps as inclusive masks, we compared the brain activity of each bimanual condition with the Usum condition to clarify the relationships between the two bimanual modes and the sum of the two unimanual modes. Table 1 shows the eight contrasts we tested. There were five possible patterns of activation level relationships that could have emerged in the analysis of activity related to BA, BS and Usum movements within the areas showing greater activation in BA than BS movements (Fig. 1b): (1) activation related to BA and BS movements could be greater than for Usum movements, (2) activation related to BA movements could be greater than for Usum movements, with similar activation for BS and Usum movements, (3) activity related to BA movements could be greater than for Usum movements, with less activation for BS than Usum movements, (4) Activation during BA and Usum movements could be similar, with less activation for BS than Usum movements and (5) activation during both BA and BS movements could be lower than for Usum movements.

Statistical analysis was conducted at two levels. First, individual task-related activation was evaluated using a general linear model (Friston et al. 1995b). Second, to make inferences at the population level, individual data were summarized and incorporated into a random-effects model (Friston et al. 1999). The spatial extent of the activation foci depicted by the height threshold of $P < 0.001$ (uncorrected for multiple comparisons) was tested, based on the theory of Gaussian random fields, which considers clusters as 'rare events' that occur in the whole brain according to the Poisson distribution (Friston et al. 1996). This procedure is used to control the family-wise error rate

Table 1 Contrasts testing the difference between initiation/continuation-related activity in bimanual movements and the sum of two unimanual movements

Time scale of activity	Condition	Contrast	Inclusive mask image
Continuation-related activity	BA > Usum	CON_BA – (CON_UR + CON_UL)	CON_BA > rest
	BA < Usum	(CON_UR + CON_UL) – CON_BA	(CON_UR > rest) U (CON_UL > rest)
	BS > Usum	CON_BS – (CON_UR + CON_UL)	CON_BS > rest
	BS < Usum	(CON_UR + CON_UL) – CON_BS	(CON_UR > rest) U (CON_UL > rest)
Initiation-related activity	BA > Usum	INI_BA – (INI_UR + INI_UL)	INI_BA > rest
	BA < Usum	(INI_UR + INI_UL) – INI_BA	(INI_UR > rest) U (INI_UL > rest)
	BS > Usum	INI_BS – (INI_UR + INI_UL)	INI_BS > rest
	BS < Usum	(INI_UR + INI_UL) – INI_BS	(INI_UR > rest) U (INI_UL > rest)

INI initiation-related activity, CON continuation-related activity, BA bimanual asymmetric condition, BS bimanual symmetric condition, UR unimanual right condition, UL unimanual left condition, Usum sum of UR and UL

(or to correct for multiple comparisons) at the cluster level. The statistical threshold was set at $P < 0.05$. We used “multi_color” software (http://www.cns.atr.jp/multi_color/) to display the functional brain maps.

Finally, we performed region of interest (ROI) analyses to precisely sort the results of the above contrasts into the five possible sets of relationships of the activity in Usum, BA, and BS (Fig. 1b). Using the results of the above contrasts as the functional ROIs, we extracted a parameter estimate (i.e., the beta weights) from each ROI for all conditions for each participant. To obtain a measure of Usum-related activity, parameter estimates were summed for the UR and UL conditions. We performed one-way repeated-measures ANOVAs with *post hoc* paired *t*-tests (two-tailed) with a Bonferroni correction for multiple comparisons to compare the parameter estimates of BA, BS and Usum in each ROI. The threshold of statistical significance was set to $P < 0.05$. Strictly speaking the ROI analysis is not completely independent from the whole-brain analysis. However, because the identified areas here were highly expected based on previous research (Sadato et al. 1997; Stephan et al. 1999; Immisch et al. 2001; Meyer-Lindenberg et al. 2002; Aramaki et al. 2006; Kraft et al. 2007), we feel that an ROI analysis is justified.

To view the qualitative temporal characteristics of the data, we extracted the time-course of the signal intensity of each ROI from the smoothed images for each participant using MarsBaR (<http://marsbar.sourceforge.net/>). These were averaged across participants.

Results

Behavior

We did not find a significant main effect of movement type on the RT of movement initiation (asymmetric movements [BA] = 743.414 ± 114.324 ms, symmetric movements [BS] =

696.526 ± 62.809 ms, unimanual right [UR] = 584.386 ± 36.087 ms, unimanual left [UL] = 667.732 ± 37.133 ms, $F[3,33] = 1.398$, $p = 0.261$) or on the mean deviation of the ITI for right-hand movements (BA = 33.601 ± 6.713 ms, BS = 23.748 ± 1.923 ms, UR = 24.436 ± 1.699 ms, $F[2,22] = 2.162$, $p = 0.139$). In contrast, there was a significant main effect of movement condition on the left-hand mean deviation of ITI (BA = 34.508 ± 4.597 ms, BS = 24.143 ± 1.443 ms, UL = 26.368 ± 2.083 ms, $F[2,32] = 4.811$, $P = 0.015$). Only the difference between BA and BS movements was significant ($P = 0.019$, paired *t*-test with Bonferroni correction for multiple comparisons), suggesting that left-hand control in the BA movement condition was less stable than in the BS movement condition.

Brain activity

Regions showing greater continuation-related activation during BA than BS movements

We searched for regions showing greater continuation-related activation during BA than BS movements. Consistent with previous studies (Sadato et al. 1997; Stephan et al. 1999; Immisch et al. 2001; Meyer-Lindenberg et al. 2002; Aramaki et al. 2006; Kraft et al. 2007), the SMA-proper, bilateral PMd, bilateral parietal, bilateral insula, bilateral globus pallidus, bilateral cerebellum and vermis were more activated in BA than BS movements ($P < 0.05$ corrected at the cluster level with a height threshold of $P < 0.001$, masked inclusively with the BA > rest image; Fig. 2a). On the other hand, we found no areas exhibiting significantly greater continuation-related activation during BS than BA movements.

Continuation-related activity for BA and BS movements in comparison with Usum movements

Using the above brain map as an inclusive mask, we compared continuation-related activity in each bimanual

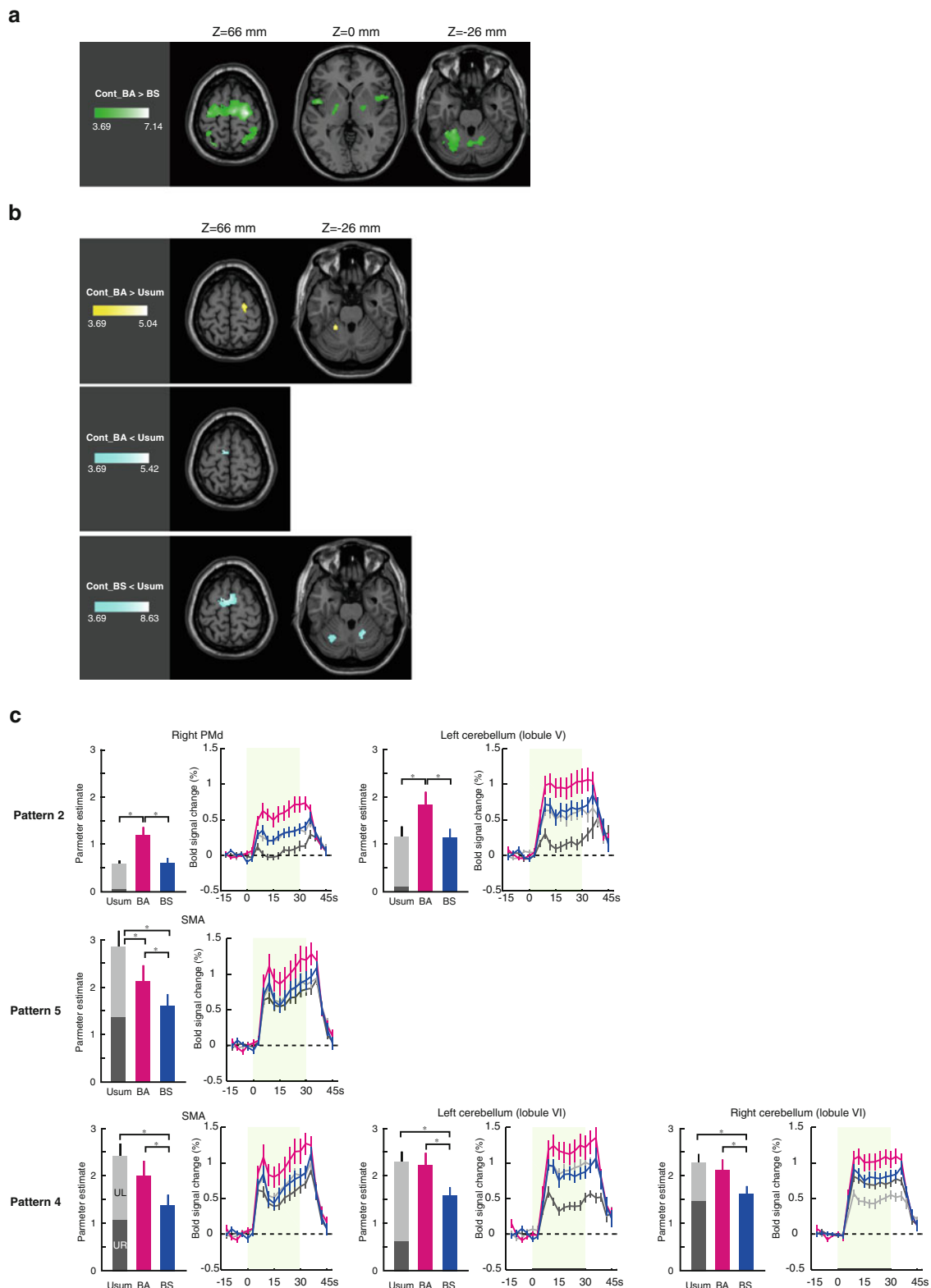


Fig. 2 **a** Brain areas showing greater continuation-related activity in the BA compared with the BS condition. **b** Brain areas showing greater continuation-related activity in the BS compared with the Usum condition (*top*), reduced activity in the BS compared with the Usum condition (*middle*), and reduced activation in the BA condition

compared with the Usum condition (*bottom*). **c** Parameter estimates and time-course plots of the *BOLD* signal in the areas shown in **b**. Error bars standard error (SE), BA magenta, BS blue, UR black, UL gray. Usum sum of UR and UL activities. * $P < 0.05$, ** $P < 0.001$

Table 2 Comparison between bimanual conditions and the sum of unimanual conditions

Time scale of activity	Condition	Side	Area	<i>x</i>	<i>y</i>	<i>z</i>	Cluster size
Continuation-related activity	BA > Usum	R	PMd	20	−10	54	222
		L	Cerebellum (lobule V)	−22	−42	−28	128
	BA < Usum		SMA	−6	−6	62	102
	BS > Usum		None				
	BS < Usum		SMA	−6	−6	58	864
		R	Cerebellum (lobule VI)	20	−56	−24	144
		L	Cerebellum (lobule VI)	−24	−60	−22	90
		L	Insula	−42	0	8	106
Initiation-related activity	BA > Usum		None				
	BA < Usum		None				
	BS > Usum		None				
	BS < Usum	L	Putamen	−20	12	2	12

$P < 0.05$ corrected at the cluster level with a height threshold of $P < 0.001$

condition with the sum of the unimanual right and left conditions (Usum) ($P < 0.05$ corrected at the cluster level with a height threshold of $P < 0.001$). Greater activation during BA compared with Usum movements was found in the right PMd and the left cerebellum (lobule V) (Table 2, Fig. 2b, top). Significantly less activity during BA than Usum movements was found in a small part of the SMA (Table 2, Fig. 2b, middle).

We found less activation during BS than Usum movements in the SMA, bilateral cerebellum (lobule VI; Table 2, Fig. 2b, bottom) and left insula (Table 2). No areas showed significantly greater activation in the BS condition compared with the Usum condition.

Patterns of continuation-related activation in each ROI

We performed ROI analyses for the areas identified above to classify the activation patterns into one of the five categories shown in Fig. 1b. Activity during BS movements in the right PMd and the left cerebellum (lobule V) was not significantly different from that during Usum movements, while activity during BA movements was significantly greater than activity related to both Usum and BS movements (Fig. 2b, top), categorized as Pattern 2 in Fig. 1b. These areas thus showed supra-additive activation, i.e., greater activation for asymmetric movements and additive activation for symmetric movement continuation, in comparison with the activity related to the continuation of two unimanual movements. On the other hand, for both BA and BS movements, a small SMA region showed significantly less activity than during Usum movements (Table 2, Fig. 2b, middle), while activity related to BA movements was significantly greater than that related to BS movements. This result is categorized as Pattern 5 in Fig. 1b. These areas showed sub-additive activation for continuation of

both asymmetric and symmetric movements. In addition, the activation related to BS movements was highly similar to the unilateral movement condition (UL; $BS = 1.393 \pm 0.220$, $UL = 1.347 \pm 0.144$, $P = 1.0$). There was no significant difference in activity between the BS and UR conditions ($BS = 1.393 \pm 0.220$, $UR = 1.082 \pm 0.149$, $P = 0.317$; paired t-test with Bonferroni correction for multiple comparisons; Fig. 2c, bottom left).

Activity in the SMA, the left and right cerebellum (lobule VI), and the left insula was significantly lower in the BS than in the Usum and BA conditions. Since no significant difference in activity was found between BA and Usum movements, the SMA, bilateral cerebellum (lobule VI), and left insula activation patterns were categorized as Pattern 4 in Fig. 1b. Thus, these areas showed sub-additive activation during symmetric movement continuation.

The time-course of the BOLD signal clearly showed 30 s of continuation activity during the task epoch (Fig. 2c).

ROI analysis of continuation-related activity in the UR and UL conditions

To investigate the characteristics of these interactions more precisely, we performed further ROI analyses to decompose Usum movements into UR and UL conditions. The activity categorized as Pattern 2 (i.e., the continuation-related activation in right PMd and left cerebellum [lobule V]) showed significant activation during UL but not UR movements (Fig. 2c top). Thus, these areas appear to be involved in left-hand control during unimanual movements.

On the other hand, the areas categorized into Patterns 4 and 5 (continuation-related activation in the SMA, bilateral cerebellum [lobule VI], left insula) showed activation significantly higher than zero in both the UR and UL

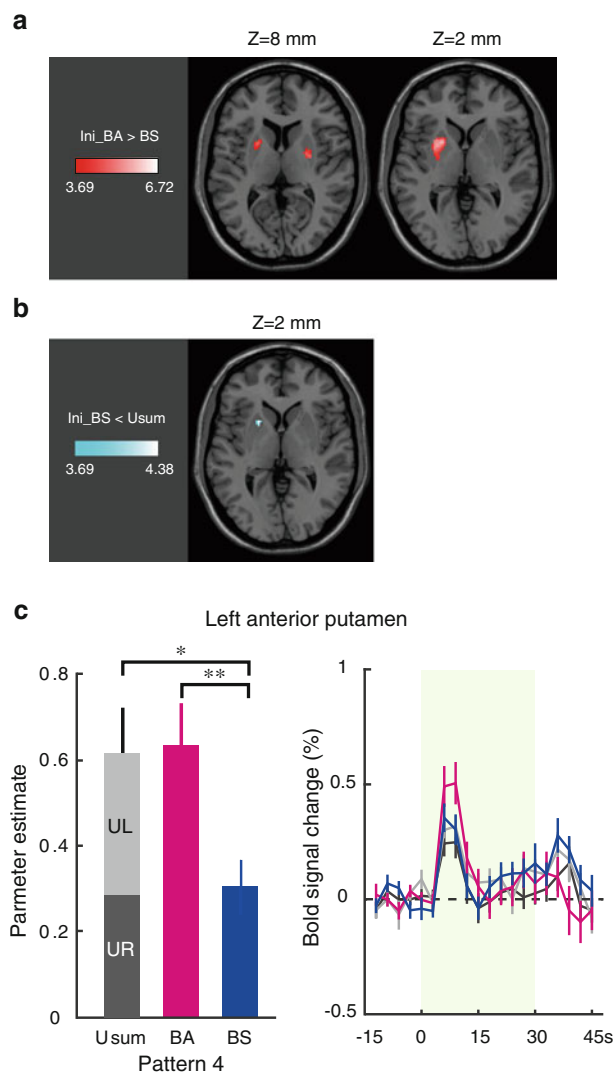


Fig. 3 **a** Brain areas showing greater initiation-related activity in the BA compared with the BS condition. **b** Brain areas showing reduced initiation-related activity in the BS compared with the Usum condition. **c** Parameter estimates and time-course plots of the *BOLD* signal in the left anterior putamen shown in **b**. Error bars standard error (SE), BA magenta, BS blue, BS blue, UL gray, Usum sum of UR and UL activities. * $P < 0.05$, ** $P < 0.001$

conditions (Fig. 2c, bottom). Thus, these areas appear to be involved in the control of both hands.

Regions showing greater initiation-related activity in response to BA compared with BS movements

The anterior to middle part of the left putamen and the middle part of the right putamen showed greater activation in response to BA than to BS movements ($P < 0.05$ corrected at the cluster level with a height threshold of $P < 0.001$; Fig. 3a). We found no areas exhibiting greater initiation-related activation during BS than BA movements.

Initiation-related activity for BA and BS movements in comparison with Usum movements

Using the above functional brain map as an inclusive mask, we compared the initiation-related activity of the two bimanual movement types to the sum of activity in response to unimanual right and left movements. We found no significant differences in initiation-related activity between BA and Usum movement conditions ($P < 0.05$ corrected at the cluster level with a height threshold of $P < 0.001$).

In contrast, we found significantly less initiation-related activation during BS than Usum movements in the left anterior putamen ($P < 0.05$ corrected at the cluster level with a height threshold of $P < 0.001$; Table 2, Fig. 3b). Meanwhile, there were no areas showing significantly greater initiation-related activation during BS than Usum movements ($P < 0.05$ corrected at the cluster level with a height threshold of $P < 0.001$).

Pattern of initiation-related activation in the anterior putamen ROI

We performed a ROI analysis for the area identified in the above comparison to classify the activation pattern into one of the five categories shown in Fig. 1b. The activity in the left anterior putamen during BS movements was significantly lower than activity during both the Usum and BA conditions. Since no significant difference was found between BA and Usum conditions, the left anterior putamen activity was categorized as Pattern 4 in Fig. 1b (Fig. 3c, left). The left anterior putamen therefore showed sub-additive activation, i.e., reduced activation during symmetric movement initiation compared with initiation of two unimanual movements. In addition, BS movements were related to only the same amount of activity as a single unimanual movement (right hand, BS = 0.305 ± 0.062 , UR = 0.2860 ± 0.0071 , $P = 1.000$; left hand, BS = 0.305 ± 0.062 , UL = 0.3304 ± 0.0056 , $P = 1.0$; Fig. 3c, left).

The time-course of the *BOLD* signal clearly showed transient activity after the onset of movement (Fig. 3c, right).

ROI analysis of initiation-related activity in the UR and UL conditions

The initiation-related activation in the left anterior putamen showed significant activation in both the UR and UL conditions (Fig. 3c). Thus, this area appears to be involved in the control of both hands.

Discussion

We demonstrated that bimanual interaction in the brain depends on specific brain areas, coordination patterns and movement phases. We found evidence of not only supra-additive interaction in asymmetric actions, in accord with previous research, but also sub-additive interaction during symmetric movements. This novel finding suggests that the human brain may save neural processing cost by using innate neural connections that allow the same information to be commonly available to both hands when they perform the same movement at the same time. This may help to reduce the number of degrees of freedom involved in bodily movements.

The PMd and SMA are both categorized as Brodmann Area 6. They are often reported together as part of the neural substrate of bimanual coordination of motor execution (Sadato et al. 1997; Meyer-Lindenberg et al. 2002; Aramaki et al. 2006; Kraft et al. 2007). However, our results showed a clear medio-lateral functional dissociation in Brodmann Area 6. The right PMd was activated supra-additively by BA movements, while the SMA was activated sub-additively during the continuation phase in both BS and BA movements.

The right PMd, which showed greater activation during BA than Usum movements, showed BS-related activation comparable to that during the continuation phase of Usum movements (Fig. 2b, top left; Fig. 2c, top left). This suggests that BA movements require extra PMd activity to maintain their unstable coordination pattern. This result lends strong support to the hypothesis that the right PMd plays a crucial role in bimanual coordination (Sadato et al. 1997; Meyer-Lindenberg et al. 2002). This finding is also consistent with a previous TMS study, in which right PMd stimulation led to a spontaneous phase transition from anti- to in-phase movement more frequently than stimulation of the SMA, left PMd or M1 (Meyer-Lindenberg et al. 2002). Moreover, the ROI analyses in the current study revealed that the right PMd was activated during UL but not UR movements (Fig. 2c, top left). This suggests that the PMd is primarily involved in controlling the left hand. Spontaneous phase transitions from asymmetric to symmetric movement often occur due to disturbances of left (non-dominant) hand movement (Semjen et al. 1995; Aramaki et al. 2006). Indeed, the mean deviation of the left-hand ITI was significantly larger for BA than BS movements. Thus, the extra PMd activation in BA movements may represent the extra demands on left-hand control, so that its movement is no longer entrained by the right-hand control system via neural crosstalk.

In contrast, we found reduced activation in the SMA during BS and BA movements compared with Usum during the continuation phase (Fig. 2b, bottom left, middle).

A unilateral SMA lesion was found to impair bimanual asymmetric movements in monkeys, and led to bimanual symmetric movements (Brinkman 1984). In humans, Chan and Ross (1988) reported that a patient with an ischemic infarction involving the right SMA was able to perform bimanual symmetric movements, but could not perform bimanual asymmetric movements (Chan and Ross 1988). These findings demonstrate that symmetric movements can be executed by the intact SMA of one hemisphere, whereas asymmetric movements require bilateral SMA activity. In this study, the amount of SMA activation during BS movements was almost the same as that in UL movements, suggesting that BS actions require no more SMA activity than single unimanual movements. These results are consistent with a previous bimanual reaching study, which reported that there was no additional SMA activity during a bimanual congruent movement (in a contrast between a symmetric movement condition and a unimanual, left-hand movement condition; Diedrichsen et al. 2006). Functionally, the SMA plays a crucial role in controlling movement timing (Halsband et al. 1993; Rao et al. 2001) and sends commands to the primary motor cortex (M1). In the M1, some neurons issue commands to bilateral homologous muscles (Aizawa et al. 1990). Thus, SMA activity may be able to reduce the effort involved in controlling the firing timing of M1 neurons more during BS than BA and Usum movements, by using M1 neurons for homologous muscle contraction, especially in BS movements. Moreover, there is evidence that the SMA is involved in rhythm and beat perception (Grahn and Brett 2007). In the current study, because the movement frequency was 3 Hz in all conditions, rhythm and beat perception would be expected to be identical in all conditions and both hands. Therefore, the brain may be able to reduce processing costs even in BA in comparison with Usum movements. This may explain our observation that the sum of two distinct unimanual activities was greater than the activity in a single bimanual condition both in BS and BA movements.

Anatomically, the cerebellum is segregated in the anterior–posterior axis by the primary fissure, which separates lobules V and VI (Schmahmann et al. 2000). We found that the cerebellum can also be segregated functionally in the anterior–posterior direction in bimanual coordination. The left lobule V was activated supra-additively during BA movements, while the bilateral lobule VI was activated sub-additively during BS movements during the continuation phase.

The anterior cerebellum, including left lobule V, which we found to show more activation during BA than Usum movements (Fig. 2b, top right), is fundamentally involved in ipsilateral motor control (Grodd et al. 2001). One of the important functions of the cerebellum is movement coordination (Timmann et al. 1999, 2001). Prior research has

demonstrated that the ipsilateral lobule V is particularly important for coordination, which is a state-dependent control process in which motor commands to one effector depend on the predicted state of another effector (Diedrichsen et al. 2007). Hence, the left anterior cerebellum would be expected to play a crucial role in BA movements, allowing the left hand to become no longer entrained by right-hand movements, functioning in a similar manner to the right PMd as discussed earlier.

The bilateral posterior cerebellum (lobule VI), which showed less activation in response to BS than Usum movements (Fig. 2b, bottom right), has been previously reported to be involved in effector-independent voluntary timing (Bengtsson et al. 2005). The control of movement timing is another important function of the cerebellum, which is thought to contain internal representations of time (Ivry et al. 1988; Ivry and Spencer 2004). During BS movements, both hands can rely on one source of timing information, using either bimanual neurons, neural crosstalk via callosal connections between the hemispheres, or the ipsilateral corticomotor pathway. Thus, common use of timing information during BS movements may reduce the processing demands on this area. This explanation may also apply to the insula, which also showed less activation in BS than Usum movements, as the insula is also important for the control of movement timing (Diedrichsen et al. 2007).

The functional mediolateral segregation we found in Brodmann Area 6 appears to correspond to the anterior–posterior segregation observed in the cerebellum. The activation pattern we found in the right PMd resembles that in cerebellar lobule V, whereas the pattern in the SMA resembles that found in cerebellar lobule VI. The PMd has been found to project to the cerebellum in monkeys (Schell and Strick 1984). The SMA also projects to the cerebellum, although it projects primarily to the basal ganglia (Wiesendanger and Wiesendanger 1985; Sakai et al. 1999, 2002). It is conceivable that the former network is involved in movement coordination, while the latter is likely to be involved in internal timing.

Previous findings suggest that the putamen is crucial for movement initiation (Kimura 1990; Romo et al. 1992; Lewis et al. 2004; Kraft et al. 2007). The putamen is anatomically segregated into three parts: the anterior, which projects to the prefrontal cortex and preSMA; the middle, which connects with the SMA; and the posterior putamen, which projects to the primary motor cortex (Lehericy et al. 2004a, b). We found that the mid- to anterior-left putamen, which has strong connections to prefrontal areas, showed greater activity in the BA compared with BS movement conditions (Fig. 3a). Moreover, a comparison with the Usum condition revealed that the left anterior putamen showed less activation during the initiation of BS than Usum movements. These results suggest that BS movements are

less taxing in terms of cognitive processes, due to the strong connections between the anterior putamen and prefrontal cortex. Before producing their first tap, participants were required to make a cognitive selection of which finger to tap first, and determine the sequence of tapping that was required. A movement plan is required to initiate BA movements in this selection process, which may proceed along the lines of the following example: ‘the first tap requires the index finger of the right hand and the middle finger of the left hand’. In contrast, for BS movements, a simpler plan such as ‘the first tap is the index finger’ may be sufficient to initiate the action, as in unimanual conditions. This means that the cognitive demands of the selection process in BS movements are the same as in unimanual movements, while BA movements can be viewed as the sum of UR and UL movements. This notion is supported by the results of the ROI analysis, which showed that BS movements required the same amount of activity as one unimanual movement, while BA movements were associated with a level of activity equal to that of Usum movements (Fig. 3c, left). Since we adopted a simple periodic finger-tapping task in which the index and middle fingers alternated, the coordination pattern could be maintained by automatic control once the movements began, using a central pattern generator-like network (Schaal et al. 2004). Thus, the transient activity of the anterior putamen associated with the cognitive selection process might be observed only in the initiation phase.

Some *limitations* of the experimental design may have affected the current results and should be considered in the interpretation of our findings.

In this study, we chose a movement frequency of 3 Hz because higher movement frequencies produce a greater difference in brain activation between symmetric and asymmetric bimanual movements (Meyer-Lindenberg et al. 2002). By using this frequency, we were able to reveal that the right PMd and left cerebellum (lobule V) are resource-demanding areas in BA movements. However, it is possible that resource-demanding interactions in other areas were missed because the high load in BA may have caused a ceiling effect of the BOLD signal in BA. This is especially likely in Pattern 3, as shown in Fig. 1. To clarify this, future studies testing lower movement frequencies will be required, in which we would expect to find no ceiling effect in the BOLD signal in BA movements.

Another potential *limitation* of this *study* is that an alternative account for the sub-additive activation we observed in the BS condition remains possible. Mechsner et al. (2001) have proposed that the perceptual bias of bimanual coordination, that is, our preference for symmetry, arises from a preference for perceptual symmetry in other modalities. Thus, the decrease of perceptual load associated with BS movement patterns might have been responsible for the

sub-additive activation we observed in the BS condition. In the present study, because participants could not see their hands, a strong effect of visual symmetry on our results would not be expected. However, clarifying the effect of perceptual preference would require a study in which hand position was manipulated. For example, brain activity in a condition with one palm up and the other down (Müller et al. 2009) could be compared with activity in bimanual conditions and the sum of unimanual conditions.

In conclusion, the findings of the current experiment confirm that bimanual interaction in the brain depends on different brain areas, coordination patterns, and movement phases. Our results indicate that this process involves not only resource-demanding interactions due to the demands of keeping non-dominant hand movements stable, but also cost-effective interactions that require no extra demands compared with unimanual movements, based on the sharing of common information between both hands. The latter finding is particularly important for increasing understanding of how actions are coordinated under the large number of degrees of freedom of the human body.

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